UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,809	07/21/2003	S. Ananth Karumanchi	01948/088004	6646

21559 7590 06/30/2006

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,809	KARUMANCHI ET AL.	
	Examiner	Art Unit	
	Ian Dang	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-12, 22, 23,24-26, 33-69* is/are pending in the application.

4a) Of the above claim(s) *11-12,22, 24-26, 33-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group II in the reply filed on April 27, 2006 is acknowledged. Applicants elected Group II, claims 1-10, 13-21, 23, 27, 28, 29-31, and 32, without traverse (MPEP § 818.03(a)).

Claims 1-10, 13-21, 23, 27-32, have been cancelled and claims 11-12, 22, 24-26, 33-40 have been withdrawn. Claims 41-69 have been added. Claims 41-69 are pending and under examination.

Claim Rejections - 35 USC § 112 (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of diagnosing a pregnant subject as having preeclampsia or eclampsia comprising measuring the level VEGF serum. However, the specification discloses several VEGF isoforms on page 23.

Applicants provide several examples of measuring VEGF levels in serum and urine of human subjects with preeclampsia or eclampsia, but do not provide sufficient relevant identifying characteristics for the VEGF polypeptides. In analyzing whether the written

description for mutants of VEGF are met for genus claims, it is first determined whether a representative number of species have been described by the complete structure. In this case, the specification discloses VEGF with VEGF biological activity (page 29) without identifying any specific structures for any members of the VEGF family.

Next it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics, special features and functional attributes that would distinguish different members of the claimed genus. Ferrera (page 796, column 1) teaches that different VEGF polypeptides have different biological functions. For instance, $VEGF_{121}$ has a 50- to 100-fold reduced potency compared to $VEGF_{165}$ for the proliferation of endothelial cells. Circulating levels for the different members of the VEGF family may be differently regulated in pregnant subject and influencing the outcome of the diagnosis. Although Applicants have identified the functional attribute for VEGF in serum, further structural studies are necessary to determine the physical and chemical attributes important for members of the VEGF family for the diagnosis of pre-eclampsia or eclampsia.

To provide adequate written description and evidence of possession of claimed genus, the specification must provide efficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure/function correlation, and other identifying characteristics. Accordingly, in the absence of sufficient recitation of distinguishing structural/physical and identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 50-67 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 41-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for rat and human pregnant female, does not reasonably provide enablement for non-human subject, such as cow, horse, sheep, pig, goat, dog or cat. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Claims 41 and 45-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for measuring free PlGF in urine and PlGF, sFlt-1, VEGF in serum, does not reasonably provide enablement for measuring PlGF, sFlt-1, VEGF in amniotic fluid or cerebrospinal fluid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Claims 68 and 69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the diagnosis of pre-eclampsia or eclampsia, does not reasonably provide enablement for the diagnosis for HELLP, IUGR, or SGA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claims 41, 44, 45, 50, 64, and 66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for urine and serum, does not reasonably

provide enablement for endothelial cells, leukocytes, monocytes, and cells derived from the placenta. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

The claims 41-69 are directed to a method of diagnosis pre-eclampsia and eclampsia in a pregnant subject by measuring levels of free PlGF in the urine. Free PlGF levels are normalized to serum levels of sFlt-1 or VEGF. Decreases in PlGF levels and changes in PAAI values are indicative of pre-eclampsia or eclampsia in pregnant subjects when compared to those of normal subject. Levels of free PlGF are determined with detecting agents. Figures 1-7 and examples 1-7 provide working examples for establishing that changes in levels of PlGF in urine and serum or sFlt-1 levels normalized with PlGF and VEGF are indicative for the diagnosis of pre-eclampsia or eclampsia in pregnant subjects.

Nature of the invention

The claims are drawn to a method for predicting pre-eclampsia by determining the level of two or more markers selected from the group consisting of PlGF, VEGF, and sFlt-1. The nature of the invention is complex given the disease is associated with several symptoms including increased blood pressure, protein in the urine, and edema. In pre-eclamptic subjects, hormonal levels are aberrantly regulated leading to abnormal levels of PlGF, VEGF, and sFlt-1 in the body of a pregnant subject. In this instant application, modulations of PlGF levels in the serum and urine may not only be a diagnosis of pre-eclampsia and eclampsia, because the angiogenic factor PlGF is also abnormally regulated in several diseases. Carmeliet et al., disclose an animal model in which modulations of PlGF levels induce changes in permeability and collateral growth in ischemia, inflammation, and cancer (page 576).

Breath of the claims

The claims are drawn to a method for predicting pre-eclampsia by determining the level of two or more markers selected from the group consisting of PlGF, VEGF, and sFlt-1. The claims encompass methods in which the sample analyzed from body fluids, such as urine blood, amniotic fluid, serum, plasma or cerebrospinal fluid disclosed in claim 66. However, Applicants only provided working examples measuring levels of these 3 growth factors in serum and urine and are enabled only for these bodily 2 fluids. The amniotic and cerebrospinal fluid may not have PlGF levels indicative of pre-eclampsia or eclampsia, because PlGF may not be able to cross the membrane barriers isolating these 2 fluids from the body.

Guidance

The specification teaches methods in which blood samples obtained from pregnant woman are assayed for the presence of the proteins PlGF, VEGF, and sFlt-1. It is determined that pre-eclampsia can be predicted in pregnant human subjects by assaying urine samples for a decrease in the combined levels of PlGF and VEGF, an increase in the ratio of PAAI index as compared to healthy/normal control pregnant subjects.

However, the specification does not teach levels of PlGF, VEGF, sFlt-1 in any type of body samples other than blood and urine samples and the levels of protein PlGF, VEGF, sFlt-1 in samples obtained from non-human subjects.

The claims 50-67 are drawn to a method for predicting pre-eclampsia by determining the level of at least one marker selected from the group consisting of free PlGF, free VEGF, and sFlt-1. The claims encompass methods in which an increase in the level of sFlt-1 or a decrease in the level of free VEGF or free PlGF polypeptide relative to a reference diagnosis is indicative

of having or having the propensity to develop pre-eclampsia or eclampsia as disclosed in claim 50. However, Applicants have not provided sufficient guidance as to what extent are increases in the levels of sFlt-1 or decreases in the level of free VEGF or free PlGF necessary for the diagnosis of pre-eclampsia or eclampsia. Any increases or decreases of the levels for any of the growth factors may be too small to have clinical significance.

Working Examples

The specification discloses methods in which PlGF, VEGF, and sFlt-1 are detected in blood and urine samples obtained from pregnant woman. The specification does not provide any working examples in which levels of PlGF, VEGF, and sFlt-1 are predictive of pre-eclampsia or eclampsia in any-non-human pregnant subjects. Levels of the growth factors PlGF and VEGF may not be regulated in a similar fashion in human subjects as in non-human subjects.

In addition, the specification does not provide working examples in which levels of PlGF, VEGF, and sFlt-1 are predictive of HELLP, IUGR, or SGA. Example 7 (page 42) HELLP is associated with pre-eclampsia or eclampsia in figure 7 (page 45), SGA is associated with pre-eclampsia or eclampsia. These 3 diseases are distinct from pre-eclampsia or eclampsia and have different etiologies. It may be that SGA and HELLP are further complications associated with pre-eclampsia may not be predictive with changes in PlGF, VEGF, or sFlt-1 levels.

Furthermore, the specification provides working examples for measuring PlGF, sFlt-1 and VEGF levels in serum and PlGF in urine. However, Applicants have not provided any working examples for measuring PlGF, sFlt-1, or VEGF levels from the group consisting of endothelial cells, leukocytes, monocytes, and cells derived from the placenta.

Amount of direction or guidance provided by the specification

The specification provides guidance on how to predictably induce proteinuria and hypertension in rats by injecting them with exogenous sFlt-1 (Example 4, page 32 and Example 5 page 37) but the rats may not have developed pre-eclampsia or eclampsia. There is no guidance that PlGF, VEGF, and sFlt-1 can be detected as an indication that the animal will develop pre-eclampsia or eclampsia as in the human case. In addition, there is no guidance provided in the specification regarding the functional activity of PlGF, VEGF, sFlt-1 in other non-human organisms, particularly no information is provided to suggest that levels of these proteins can be used to diagnose pre-eclampsia or eclampsia. Thus, the teachings in the specification regarding the human condition are not predictive of pre-eclampsia or eclampsia in rats and other non-human subjects (including , e.g., a cow, a horse, a sheep, a pig, a goat, a dog, or a cat) (page 7) because human reproductive physiology is different from the non-human subjects. For instance, human hormonal level profiles during pregnancies have distinctive characteristics from the ones of animals.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

Therefore, due to the breath of the claims and the amount of guidance, and the lack of working examples, the examiner has determined that one skill in the art would not know how to make/use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 45-47, 57-67 and 50-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 45 is indefinite because the claim does not recite a clear link between the method of diagnosing a pregnant subject with pre-eclampsia or eclampsia, and as to what constitute a diagnosis for pre-eclampsisa or eclampsia. The claim does not provide with a clear determination as to what the step needed for the diagnosis of pre-eclampsia or eclampsia. The measurements alone for levels of sFlt-1 PlGF, and VEGF do not provide a diagnosis of the disorder. Thus the metes and bounds of the claims cannot be determined.

Claims 50 and 51 are indefinite because the claims do not recite a clear link between the method of diagnosing a subject with pre-eclampsia or eclampsia and as to what constitute a diagnosis for pre-eclampsia or eclampsia. The claims do not provide a clear determination as to what constitute a significant increase in the level of sFlt-1 or a significant decrease in the level of free VEGF or free PlGF polypeptide indicative for the diagnosis of pre-eclampsia or eclampsia. Applicants have not provided any definite values to be indicative of pre-eclampsia or eclampsia.

In addition, claims 52 and 53 are indefinite because the claims do not provide any indication regarding how an alteration or an increase in the metric PAAI value is indicative for the diagnosis of pre-eclampsia or eclampsia. Applicants have not provided any definite values or ranges for PAAI to be indicative of pre-eclampsia or eclampsia. Thus the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 43, 45, 46, 49, 56-60, and 62-65 are rejected under 35 U.S.C. 102(b) as being anticipated by Charnock-Jones et al. (WO 98/28006; published July 2, 1998; filed December 22, 1997; included on the IDS on page 2 received on February 9, 2005).

Charnock-Jones et al. teach that maternal serum samples for pre-eclamptic women has significantly lower concentrations of PlGF (150-185 pg/ml) when compared to those of healthy controls (500 pg/ml) (page 12). In addition, PlGF levels are significantly lower in women who go on to develop pre-eclampsia, and that the distinction between normal women and those at risk of developing pre-eclampsia can be made at an early stage of pregnancy (e.g. by 25 weeks in nearly all cases, and as early as 16-20 weeks for some women). The disclosure of Charnock-Jones et al. encompasses the limitations of claim 43 regarding for the diagnosis of pre-eclampsia or eclampsia in a subject with PlGF polypeptide levels less than 400 pg/ml at midgestation.

Charnock-Jones et al. teach a method of for the diagnosis of a hypertensive disorder, which includes pre-eclampsia or eclampsia. On pages 3 and 4, the specification of Charnock-Jones et al. disclose that pre-eclampsia or eclampsia is a hypertensive disorder of interest. Claim 14 discloses a method of diagnosing a hypertensive disorder comprising by first measuring the amount of VEGF and secondly determining the amount of soluble VEGF receptor or sFlt-1 disclosed in claims 15 and 16. Thus, claims 14-16 disclosed by Charnock-Jones et al. embrace the limitations of claim 45 disclosed in the instant application teaching the diagnosis of

pre-eclampsia or eclampsia by measuring the levels of at least two of sFlt-1, free VEGF, and free PlGF polypeptide.

In addition, on page 35 of the specification, Charnock-Jones et al. recite that a diagnostic and/or predictive test could be based on the determination of the amount of any one of PlGF, VEGF or sFlt-1 in women. The ratio of any two or more of levels of growth factors may be more informative or predictive than absolute levels of the substances. The disclosure matches the limitations of claims 46 and 49 of the instant application.

Moreover, Charnock-Jones et al. disclose that the levels of PlGF and VEGF of pre-eclamptic of pregnant women are compared to control subjects, who are normotensive pregnant women (page 34). These teachings match the limitations of claims 56 and 57.

Finally, on pages 34-35 in the specification of Charnock-Jones et al. recite that the levels of PlGF and VEGF are measured from plasma separated from blood collected from pregnant women at different stages of gestation (from 15 week of gestation until term). The measurements are done with the immunological assay ELISA. These disclosures embrace the limitations of claims 58, 59, 60, 62, 63, 64, and 65

Thus claims 43, 45, 46, 49, 56-60, and 62-65 are anticipated by the disclosure by Charnock-Jones et al.

Conclusion

No claims are allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ian Dang whose telephone number is (571) 272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
June 20, 2006

Marianne P. Allen
MARIANNE P. ALLEN
PRIMARY EXAMINER
6/20/06
AU1647